Health-Related Quality of Life of Patients with HPV-Related Cancers in Indonesia

Setiawan, Didik; Dusafitri, Arrum; Galistiani, Githa Fungie; van Asselt, Antoinette D.I.; Postma, Maarten J.

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Abstract

Background HPV-related cancer becomes a serious concern in developing countries. Valid estimates of a country-specific health-related quality of life (HRQoL) for patients with HPV-related cancers provide a substantial tool in determining the burden of the disease.

Methods HRQoL of patients with HPV-related cancers (cervical, uterine, nasopharyngeal, head and neck, and anogenital cancer) was assessed using the EQ-5D questionnaire. Validity and reliability were assessed by means of construct validity and test-retest reliability methods, respectively. Subsequently, the EQ-5D utility index was calculated using the Thailand value set.

Results The EQ-5D questionnaire came out as a valid and reliable questionnaire for measuring HRQoL of patients with HPV-related cancers in Indonesia. From a total of 520 patients diagnosed with HPV-related cancers, 404 patients were excluded due to inclusion criteria and finally 116 patients participated in the study. Mean age of the patients was 47.5 years (SD=12.03). Most of the patients were female (56.0%), married (97.4%), and less than half of them had finished high school (32.7%). Moreover, the proportions of nasopharyngeal, cervical, head and neck, anogenital, and uterine cancers in the study population were 29.3%, 24.6%, 22.4%, 14.2% and 9.5%, respectively. The average HRQoL of the HPV-related cancers was 0.69 (SD 0.10) with the highest and lowest estimates applying to uterine cancer (0.84 ± 0.29) and head-and-neck cancer (0.58 ± 0.33), respectively.

Conclusion In comparison to existing reference utility index for healthy population, HRQoL of patients with HPV-related cancers was found to be reduced to a certain extent in our study for Indonesia.

Keywords Health-related Quality of Life, Indonesia, HPV-related cancer, cervical cancer, human papillomavirus

Introduction

Human Papillomavirus (HPV) infections are a well-established cause of not only cervical cancer (1–4) but also other cancers, including head and neck, anogenital (anus, vulva, vagina and penis), uterine, and nasopharyngeal cancers (5,6). In addition, the global burden of HPV-related cancer is increasing and developing countries, including Indonesia, bear a high proportion of this burden (7). For example, data reported by the Ministry of Health in Indonesia showed that HPV-related cancers, especially cervical and nasopharyngeal cancer, were among the 10 cancers with the highest incidence and mortality rate in Indonesia (8).

Various health technologies such as chemotherapy (9,10), prevention strategies (11–14), new hormonal therapies (15,16), and clinical practice guidelines (17) are constantly developed and changed to combat cancer. The implementation of these health technologies have resulted in a wide range of improvements in outcome measures, with success being influenced by cancer type, study site, outcome measure, or even the cancer treatment and prevention itself (18,19). However, various, and sometimes life threatening, side effects from the treatments could possibly occur and both those health technologies and their side effects occasionally influence not only the health status of the patients but also their social and emotional well-being.

Within this broad variety of issues, the need for comparability of outcomes has been recognized and the term 'health related quality of life' (HRQOL) for this purpose is widely accepted (20,21). HRQOL generally captures the complete health state of an individual since it includes several important health parameters from, for example, physical, psychological and social health dimensions (22). Any reduction in the value of HRQOL reflects a reduction of the health of the individual. Therefore, HRQOL is able to convey important information for assessing the overall burden of a disease and the effectiveness of interventions as well.

With regard to cancer disease, HRQoL measurement tools may be classified into *generic*, *general cancer*, and *cancer-site-specific* or *cancer-problem-specific*. General cancer-, cancer-site-specific and cancer-problem-specific HRQoL measurement tools generally provide more detailed information in a single cancer-type or cancer-related problem, while an ultimate advantage of generic HRQoL measurement tools is that, because they can be implemented over a wide range of conditions and interventions, enable comparison of outcomes across diseases (23,24). One example of a generic questionnaire is the EuroQoL-5 Dimension (EQ-5D) questionnaire which is developed by the EuroQoL group and widely used across the world (25–27). Further advantages of the EQ-5D questionnaire are that it has only five questions and it is easy to administer and complete. There are two types of EQ-5D questionnaires: the 3 level EQ-5D (EQ-5D-3L) and the more recently developed version with 5-

levels (EQ-5D-5L). Several studies support both the validity and sensitivity of the EQ-5D questionnaire in cancer patients (24,28). However, some studies suggest that the 5-level classifier system has less ceiling effect and better discriminative abilities with potentially more power to detect differences between groups as compared to EQ-5D-3L (29,30).

Indonesia-specific HRQOL of HPV-related cancers provides initial information in decision making processes since it will assist subsequent studies such as cost-utility analyses. Subsequently, this will allow for comparing outcomes of interventions for HPV-related cancer with the outcomes of other interventions, within as well as outside the area of HPV-related cancers. The purpose of this study is to investigate the HRQOL of HPV-related cancer patients in Indonesia, using the EQ-5D-5L.

Methods

A descriptive cross-sectional study was performed, directed at the HRQOL of HPV related cancer patients in Indonesia. The study was divided into two main activities, consisting of pilot testing and the main study. Notably, this study was approved by the ethics committee of the Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Pilot study

Initially, a pilot study was performed to evaluate the validity and reliability of EQ-5D questionnaire for patients with HPV-related cancers in the specific Indonesian setting. A convenience sample of 30 patients with HPV-related cancers was recruited from Dadi Keluarga public hospital, Purwokerto, Indonesia. On the recruitment day (day 0), patients filled out both the EQ-5D-5L questionnaire and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30, a cancer-specific questionnaire. On day 14, patients filled out the EQ-5D-5L a second time.

As mentioned, the EQ-5D questionnaire is a generic QoL instrument developed by the EuroQoL group, and contains five questions and a visual analogue scale (VAS). The questions comprise 5

different dimensions i.e. mobility, self-care, usual activities, pain/discomfort and anxiety/depression. We adopted the updated version of EQ-5D, containing 5 levels of severity on each dimension since it was considered to be more sensitive and reliable compared to the previous 3-level version (EQ-5D-3L). In addition, the VAS records patient's self-rated health perception, graded between 0 (worst) and 100 (best).

The EORTC QLQ-C30 is a disease specific questionnaire developed mainly to assess cancer patients´ quality of life. It consists of 3 different scales: functional (15 questions), symptoms (13 questions) and global quality of life (2 questions). The EORTC QLQ-C30 was chosen as the comparator in the validation process as the Indonesian-translated version has been validated (31) and some questions, particularly global health status, physical functioning, role functioning, emotional functioning and pain, have been identified as significant predictors of EQ-5D outcomes according to several mapping studies (32–35). Therefore, construct validity testing, i.e. assessing whether the EQ-5D questionnaire can be interpreted as a meaningful measure of quality of life, was performed by measuring the correlation between each mapped question ofEQ-5Dand EORTC QLQ-C30 as they have the same construct (convergent validity method) (36). Each of EORTC QLQ-C30 subscales was considered to be correlated with an EQ-5D dimension when the Pearson correlation coefficient statistically significantly indicated so (32,34,35). Furthermore, the value of the Pearson correlation represents the magnitude and direction of the correlation (37).

In order to assure the reliability of the EQ-5D questionnaire, the two measurements (day 0 and day 14) were compared within patients in order to assess test-retest reliability (38). This method was chosen as in cancer patients, significant changes in quality of life rarely occur within a 14-day interval and although a clear recommendation to avoid recall bias is scarcely available and often debatable, this 14 days interval is considered sufficient to avoid recall bias (39). Test-retest reliability represents measurement stability, using the Intra Class Coefficient (ICC) (40,41). ICC values were interpreted as follows: weak agreement if the ICC is lower than 0.40, good agreement if the ICC lies between 0.40

and 0.75 and excellent agreement if the ICC is 0.75 or higher (41). Additionally, Cronbach's alpha was calculated to assess internal consistency, i.e.to determine whether the EQ-5D questions together measure the same construct of HRQoL of HPV-related cancer patients. Internal consistency was considered to be good if Cronbach's Alpha was higher than or equal to 0.80 (38).

Main study

All registered patients from 2010 to 2015 in Margono public hospitals, Purwokerto, Indonesia, were screened for their eligibility. Inclusion criteria were: over 18 years old, diagnosed with any HPV-related cancer (cervical cancer, uterine cancer, nasopharyngeal cancer, head and neck cancer, or anogenital cancer) and having received any care in the hospitals. Patients with chronic disease comorbidity were excluded. A clinical convenient sample was implemented for all patients who were eligible, received and signed informed consent before both the EQ-5D and the EORTC QLQ-C30 questionnaire were filled out while the patient's sociodemographic and clinical information - such as age, sex, education level and diagnosis of cancer - were collected from medical records. These two separate datasets were matched according to the medical record number for each patient.

Each dimension of EQ-5D-5L is presented as a dichotomous outcome: no problem (answer level 1) or problems (answer levels 2 to 5). Furthermore, a major outcome provided by the EQ-5D questionnaire is an index-based-value (utility index) allowing calculation of Quality Adjusted Life Years (QALYs)(42). This utility index, ranging from lower than 0 (worse than death) to 1 (perfect health), is generated by transforming patients' responses to the five questions, using a country-specific value set. Since an Indonesia-specific value set is not available yet, the utility index was calculated using the Thailand value set and subsequently presented by cancer type(43).

Statistical analysis was performed in order to identify the differences of both value EQ-5D utility index and EQ-5D VAS based on the study characteristics and cancer groups. Since the results of normality test using Shapiro-Wilk showed that both parameters were not normally distributed (p value of 0.000 for both parameters), a non-parametric test was implemented. The Mann whitney U

test was used for gender and marital status; while the Kruskal-Wallis H test was used for education level and cancer groups.

Results

Pilot study

Age of the patients in the pilot study ranged from 22 to 68 years with a mean of 51.5 years and SD at 11.5 (data not shown). Most of the patients were female (56.7%) and diagnosed with head and neck cancer (70.0%), followed by cervical at 13.4% and nasopharyngeal cancer at 10.0% (data not shown). According to the ICC coefficient generated from test-retest reliability, each subscale in the Indonesian version of the EQ-5D questionnaire had an excellent agreement (≥0.75). The EQ VAS scores had a good agreement with an ICC coefficient of 0.73. Additionally, EQ-5D had a good internal consistency as the value of Cronbach's Alpha was higher than 0.80 (Table 1).

There were significant relationships between almost all dimensions of the Indonesian version of the EQ-5D with mapped subscales of EORTC QLQ-C30 including physical function, role function, fatigue and pain. Only the mobility subscale of the EQ-5D seemed uncorrelated with social functioning on the QLQ-C30. Meanwhile, the EORTC QLQ-C30 global health status subscale only correlated with the EQ-5D anxiety/depression dimension, whereas cognitive function only correlated with pain/discomfort. The EQ VAS of EQ-5D was apparently correlated with all EORTC QLQ-C30 subscales except cognitive function (Table 2). Strong correlations were generated by some dimensions of the EQ-5D and subscales of the EORTC QLQ-C30, such as between self-care & physical function, usual activities & physical function and pain & discomfort, with correlation coefficients of -0.870, -0.55, and 0.842, respectively.

Main study

From the hospital database, the total of 520 patients could be identified for this study of whom 374 were eligible for inclusion and subsequently, if possible, visited at their home. Finally, 116 patients were included in the study (figure 1).

Mean age of the patients was 47.5 years (SD=12.03, range 18-75). Most of the patients were female (56.0%), married (97.4%), and less than half of them had finished high school (32.7%). Moreover, the proportions of nasopharyngeal, cervical, head and neck, anogenital, and uterine cancer in the study population were 29.3%, 24.6%, 22.4%, 14.2% and 9.5%, respectively (Table 3).

The statistical analysis showed that utility index was not statistically significantly different with respect to most of the patients' characteristics at baseline, except for education level (*p value* 0,039). However, since the analysis was performed using non-parametric methods, the specific differences among each group could not be identified. Furthermore, the EQ-5D VAS was not statistically significantly different with respect to patient characteristics.Based on information collected using the Indonesian version of the EQ-5D 5L questionnaire (Table 4), the highest reduction on the mobility dimension was seen with cervical cancer (46.42%). With regard to the self-care dimension, only few patients with HPV-related cancers (<20%) encountered problems. Meanwhile, almost half (41.38%) of the patients reported difficulties on the usual activity dimension. Problems on the pain/discomfort dimension were heterogeneous. Nasopharyngeal patients reported a high proportion of pain/discomfort issues (67.65%) while none of uterine cancer reported pain/discomfort. In addition, a high proportion of patients with nasopharyngeal cancer (55.88%), cervical cancer (53.85) and anogenital cancer (53.57%) experienced problems on anxiety/depression.

The overall value of EQ-5D VAS for all patients included with HPV-related cancers was relatively high (77.38 ± 6.42) ranging from 72.05 ± 25.55 to 88.54 ± 14.60 for anogenital cancer and uterine cancer, respectively. Also, the utility index was also moderately high for the overall patient population included (0.69 ± 0.10). The highest value for the EQ-5D utility index was found in uterine cancer (0.84 ± 0.29), followed by nasopharyngeal cancer (0.75 ± 0.30), anogenital cancer (0.68 ± 0.35), cervical

cancer (0.61 ± 0.39) and head and neck cancer (0.58 ± 0.33). finally, the Kruskal-Wallis H test showed that both utility index and VAS were not statistically significantly different since the *p values* were 0.059 and 0.144, respectively.

Discussion

Our study shows that there is a various reductions in HRQoL of each patients with HPV-related cancers in Margono hospital, Purwokerto, Indonesia. Although the reference utility index for the healthy population in Indonesia is not available yet, two studies showed that the utility index in a healthy population in Sri Lanka and south Australia was 0.85 (CI 95%CI 0.84-0.87) and 0.91 (95%Ci 0.90-0.91), respectively . These findings are apparently congruent with a study from Australia that suggested that HRQoL of HPV related cancer ranged from 0.57 to 0.79 (44). In particular, our finding on head and neck cancer mimics studies from Italy (0.69 ± 0.30) and Australia (0.58 ± 0.50), but those findings were considerably lower than found in a study from Canada (0.83 ± 0.14) (44–46). Several studies in cervical cancer patients reported similar utility index, such as an Italian study (0.58 ± 0.31), a study in the US (0.68) and a study in another region of Indonesia using the EQ-5D-3L questionnaire and the Malaysia value set (0.76 ± 0.20) (45,47,48). Furthermore, the utility index for anogenital cancer and nasopharyngeal cancer from this study was slightly higher compared to what was found in Italy (0.50 ± 0.26) and in Australia (0.58 ± 0.05), respectively (44,45). The differences in utility index across studies might be caused by several issues including different perception of health across populations and countries as partly represented by the different value sets (49), several characteristics including age and education (50), and also the use of different EQ-5D questionnaires (notably, 5L and 3L) (30,51).

According to our study, the most commonly reported problems by all types of patients with HPV-related cancers were pain/discomfort followed by anxiety/depression. These findings were considerably strengthened by previously published studies on cervical cancer (48) and gynecological

cancer (31) patients in Indonesia using the EQ-5D and EORTC QLQ-C30 questionnaires, respectively. The finding of zero cases of pain/discomfort reported by uterine cancer patients may have been caused by the small number of patients, or the fact that patients were fully adapted to their condition. However, most studies on HRQoL in cancer patients explained that the pain/discomfort dimension had the highest proportion of problems reported in comparison with other dimensions in the EQ-5D questionnaire (25,27,52,53). Although several recommendations on cancer-related pain management exist (17,54), cancer-related pain, commonly caused by both the cancer itself and cancer treatment, is still an important issue (55,56).

EQ-5D was found to be a reliable and valid instrument for measuring HRQoL in HPV-related cancers in Indonesia, as evidenced by excellent agreement on test-retest reliability (ICC ≥ 0.75 for all dimensions) and strong correlations with most of the dimensions of EORTC QLQ C30. EORTC QLQ-C30 was chosen as comparator on the validation process since it has been mapped for each dimension in EQ-5D for cancer patients (35). Furthermore, our methods and results were consistent with other EQ-5D validation reports in several diseases and countries including cervical cancer in Taiwan (27) and chronic diseases (cardiovascular disease, respiratory disease, depression, diabetes, liver disease, personality disorders, arthritis, and stroke) in a multi-country setting (30).

EQ-5D was chosen since this questionnaire provides a single utility index and has several advantages, including its brevity and ease of administration, and the availability of previous mapping exercise results. Also, it is recommended by several guidelines (32,35,57–59). The utility index produced by EQ-5D provides a simpler comparison between interventions for different health problems than other patient-specific or disease specific questionnaires such as the *Patient Generated Index* or *The Cancer Patient Experiences Questionnaire* (CPEQ) (60,61). Furthermore, the implementation of utility information for economic evaluation is generally acceptable, quite often even required, for health technology assessment processes in almost all regions in the world.

Although the prevalence of chronic diseases in cancer patients is substantial (62), we excluded patients chronic diseases' comorbidity since several studies showed that chronic diseases, such as stroke, COPD or chronic kidney disease, significantly further decreases HRQoL in cancer patients (50,63–65), A study from Serbia showed that cancer patient with complications showed a higher level of depressive symptoms (65). There was also a substantial reduction on physical and social functioning of breast cancer patients with chronic disease complications (50). Although an Indonesian-specific HRQoL estimate with respect to the influence of chronic disease complications in cancer patients would be generally interesting, this would require a substantially larger sample size.

One of the limitations of this study was that the cancer sub-stages could not be presented because the medical records or hospital database did not provide sufficient information for this. Cancer staging is valuable information in cancer treatment since guidelines generally provide treatment recommendations based on cancer stage. Since the information about sub-stage of each cancer was lacking, it is not possible to say what caused this not reporting of pain/discomfort reported by uterine cancer patients. It may indeed be that most patients were in the early stage of cancer. A possible explanation for the unavailability of data on cancer stage is that the documentation process in the hospitals concerned might not be standardized; there may even be a lack of Standard Operating Procedures (SOPs) altogether in this area. An Indonesia-specific EQ-5D value set for the 5-level version is not available yet. Therefore, we converted the descriptive information produced by the questionnaire into a health utility index by using the value set from Thailand (43). The Thailand-specific value set was chosen because Indonesia and Thailand have several similarities including social, cultural and economic factors. Moreover, the adoption of another country's value set is practically acceptable (66).

As the patients data were collected from a single public hospital in Central Java, the generalizability of the result coul be considered questionable. However, Margono Public Hospital, can be considered as being representative of a public hospital that provides services for cancer patients at the district

and province level in the Indonesia region. According to the data from the Ministry of Health, every province has, at least, 1 hospital which has comparable characteristics with Margono public hospital. In addition, an analysis in terms of demographic information for respondent versus non-respondent patients could increase the generalizability of the results, therefore, further study should also collect the data from non-respondent patients.

The descriptive cross sectional approach performed in this study limits the amount of information provided. Further research adopting a comparative cohort study could be an interesting option for providing the complete picture, including the ratio of HPV-related cancers' utilities indexes compared to a healthy population in Indonesia. Nevertheless, this study provides a significant addition to the literature on HPV-related cancers' utility values in Indonesia, by implementing a valid and reliable questionnaire and coming up with findings mostly consistent with various other studies in the same field in other regions of the world.

Further research into the HRQoL of patients with pre-cancer, sub-stages of cancer or even HPV-related genital warts is worthwhile in completing the information on the full scale of consequences of HPV infection in Indonesia. In terms of the decision making process, a cost-effectiveness analysis on HPV related cancer prevention strategies using our findings will provide useful information for decision makers in Indonesia.

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Compliance with Ethical Standards:

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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